Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 11-22 and 63-120 are pending in the application, with claims 63, 71, 91, and 107 being the independent claims. These changes are believed to introduce no new matter, and their entry is respectfully requested. Support for the amendments can be found at least in the cancelled claims and throughout the specification. Specifically, support for amended claims 63 and 111 can be found, *inter alia*, at pages 20 and 24.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

The Rejection under 35 U.S.C. § 112, First Paragraph, Written Description

The Examiner has rejected claims 11-21 and 63-120 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. Applicants respectfully traverse this rejection.

The Examiner has taken the position that:

> Applicants were not is [sic] possession of an M-MLV RT enzyme as a starting material for further mutational studies, and point mutations introduced into the RNAse H domain of a 684 amino acid reverse transcriptase encoded by the pRT601 vector (further referred to as pRT601 RT) were not proven to possess reduced RNAse H activity. It is also not

> clear what was the starting material for further mutational analysis.

Office Action, page 3, lines 8-12.

The Examiner further adds "[w]hile some mutations are defined, such as the ones cited above, the rest of the surrounding sequence of 683 amino acids is not defined." See Office Action, page 4, lines 9-11. Applicants respectfully but emphatically disagree.

The analysis of whether the specification complies with the written description requirement calls for the examiner to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention. Such a review is conducted from the standpoint of one of skill in the art at the time the application was filed *(see, e.g., Wang Labs. v. Toshiba Corp.,* 993 F.2d 858, 865, 26 USPQ2d 1767, 1774 (Fed. Cir. 1993)) and should include a determination of the field of the invention and the level of skill and knowledge in the art.

Moreover, what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d at 1384, 231 USPQ at 94. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. *See, e.g., Vas-Cath,* 935 F.2d at 1563, 19 USPQ2d at 1116*; Martin v. Johnson,* 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [*i.e.*, "in the same words"] to be sufficient."

The Examiner appears to be confused with regards to the RNase H activity of Superscript™ II. The specification indicates that:

> All mutant reverse transcriptases tested also contained the

> point mutations to remove RNase H activity, as in SuperScript II (SS II, U.S. Patent Nos. 5,244,797; 5,405,776; 5,668,005 and 6,063,608). Point mutations were made in the M-MLV RT gene to remove RNase H activity. The point mutations include D524G, D583N, and E562Q.

Specification, page 52, lines 9-13. Applicants also provide herewith a copy of the SuperScript™ II Technical Bulletin which further indicate that SuperScript™ II lacks RNase H activity (referenced herein as IDS document AS37). Thus, contrary to the Examiner's assertion, it is clear that point mutations introduced into the RNase H domain do in fact exhibit reduced RNase H activity.

Further, the present specification provides a number of examples of mutant reverse transcriptases that can be used in the practice of the invention. *See, e.g.,* page 29, Table 1. The sequences of these exemplary reverse transcriptases including M-MLV are known in the art. Publications describing such reverse transcriptases have been incorporated into the specification by reference. *See, e.g.*, specification page 29, paragraph 0082, and page 65, paragraph 0160. In addition, the specification identifies mutants with the required functional characteristics, *i.e.*, increased fidelity, reduced or eliminated misincorporation, and reduced or substantially reduced terminal deoxynucleotidyl transferase activity (*see, e.g.,* specification, page 53, Table 2, Examples 1 and 2, and Figures 1-4).

Moreover, the specification identifies the relevant structural features that correlate to these functional characteristics. For example, the regions corresponding to areas of fidelity which may interact with template-primer during nucleic acid extension are provided for a number of reverse transcriptases, including M-MLV (*see, e.g.,* specification, page 19, paragraph 0058 and page 7, Table 1). The specification also provides guidance as to the types of mutations that can be introduced in the thumb,

fingers and palm regions of at least two exemplified reverse transcriptases (HIV and M-MLV) in order to impart particular physical and functional characteristics of the claimed reverse transcriptases (*see, e.g.,* specification page 19, paragraph 0058, page 27, paragraph 0080, and page 29, Table 1). The specification further teaches specific assays to determine the activities of these RTs, *i.e.*, increased fidelity, reduced or eliminated misincorporation of nucleic acids, and/or reduced terminal deoxynucleotidyl transferase activity. *See, e.g.*, Examples 1-3 and Figures 1-4.

Applicants respectfully submit that based on the disclosures contained in the present specification, one of ordinary skill in the art would readily recognize that Applicants, at the time the present application was filed, had possession of the claimed invention. Reconsideration and withdrawal of this rejection are respectfully requested.

The Rejection under 35 U.S.C. § 112, First Paragraph, Enablement

The Examiner has rejected claims 11-21 and 63-120 under 35 U.S.C. §112, first paragraph, because the specification is allegedly not enabled for the full scope of the claims (Office Action, pages 4-7). Applicants traverse this rejection.

The Examiner contends that:

> [d]ue to the large quantity of experimentation necessary to determine all possible mutations in all possible M-MLV reverse transcriptases which will result in increased enzyme fidelity, the lack of direction and guidance presented in the specification regarding creation of all possible mutations in all possible M-MLV reverse transcriptases which will result in increased enzyme fidelity, the absence of working examples directed to making such mutations in M-MLV reverse transcriptases, the unpredictability of the effects of mutations on protein structure and function (see references below), undue experimentation would be required

> of the skilled artisan to make and use the claimed invention in its full scope.

Office Action, page 6, lines 14-21. Applicants respectfully but emphatically disagree.

In proceedings before the United States Patent and Trademark Office, the Examiner bears the initial burden of proving that a specification is non-enabling. *In re Marzocchi*, 439 F.2d 220, 223-24 169 USPQ 367, 370 (CCPA 1971). A specification is presumed to be enabling unless the Examiner provides acceptable objective evidence or sound scientific reasoning showing that it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention. *Id.*

The proper standard of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the application, coupled with information known in the art, without undue experimentation. *See United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), citing *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 107 S. Ct. 1606 (1987). The question of undue experimentation is a matter of degree, and "the key word is 'undue,' not 'experimentation.'" *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), quoting *In re Angstadt*, 190 USPQ 214, 219 (C.C.P.A. 1976). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation must not be unduly extensive. *PPG Indus., Inc. v. Guardian Indus. Corp.*, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996), citing *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 224 USPQ 409, 413 (Fed. Cir. 1984).

In the present case, the specification clearly sets forth which mutations in specific regions of M-MLV RT and other viral RTs may be made to achieve the claimed invention. *See, e.g.*, the Examples and Table 1. The Examiner clearly acknowledges this

enabling disclosure by stating:

> [t]he following facts are presented in the specification: 1) mutations Y64W, R116M, K152R, Q190F, T197A and V223H resulted in RTs with increased fidelity and lower degree of nucleotide misincorporation (Table 2, [0140], [0141]); 2) mutations F309N, T197E and Y133A resulted in RTs with decreased TdT activity ([0142], [0149]), 3) mutant RTs with H204R+Y306K, H204R+Y306K+F309N mutations had increased fidelity ([0142]), and 4) mutations F309N and F309/V223H had increased fidelity as well.

Office Action, page 5, lines 8-14. The Examiner appears to be concerned with the other possible mutations for each amino acid position. However, the Examiner is reminded the Federal Circuit has held that "[t]he enablement requirement is met if the description enables any mode of making and using the invention." *Johns Hopkins University v. CellPro, Inc.,* 152 F.3d 1342, 1361 (Federal Circuit 1998). "[T]he law makes clear that the specification need teach only one mode of making and using a claimed composition." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.,* 126 F.Supp.2d 69, 160 (D. Mass. 2001). Clearly, the specification discloses several modes of generating reverse transcriptases with increased fidelity thereby exceeding the standards under *Johns Hopkins University* and *Amgen*.

Moreover, Applicants are not limited to the confines of the specification to provide the necessary information to enable the invention. One of ordinary skill in the art is deemed to know not only what is considered well known in the art but also where to search for any needed starting materials. *In re Howarth*, 654 F.2d at 106, 210 U.S.P.Q. at 692. In addition, Applicants may also incorporate by reference the necessary information by citing to certain types of documents that contain this information. *Id.* The specification clearly exemplifies all the requirements of an enabling disclosure as set

forth by *Howarth*. *See, e.g.*, pages 29, 52, and 53-65. Therefore, contrary to the Examiner's contention, the specification is enabled for the invention as claimed. Reconsideration and withdrawal of this rejection are respectfully requested.

The Rejection under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 11-22, 63-70 and 111-115 under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Applicants traverse this rejection.

Specifically, the Examiner contends that "to increase fidelity" in claim 63 is indefinite because "no standard for comparison is provided." Applicants respectfully disagree.

Claim 63 recites an M-MLV reverse transcriptase which has been mutated to increase fidelity compared to the corresponding unmodified reverse transcriptase, with the proviso that said mutation is not at amino acid position Tyr222.

The specification distinctly points out what corresponding unmodified enzyme to use for comparison. *See, e.g.,* specification, page 20, paragraph 0061. Further, the examples clearly indicate that a comparison may be made to the SuperScript™ II enzyme which contains three point mutations to remove the RNase H activity. *See, e.g.*, specification page 52, lines 9-13, Examples 1 and 2, and Figures 1-4. Therefore, the claims clearly comport with the requirements of 35 U.S.C. §112, second paragraph. Withdrawal of this portion of the rejection is respectfully requested.

The Examiner further contends that no definition has been provided in the specification for "reduced or substantially reduced RNase H activity" or how to determine it. See, Office Action, page 8, lines 2-3. Applicants respectfully disagree.

Applicants have amended claim 111 to remove "reduced" from the claim thereby rendering moot this portion of the rejection. The specification clearly teaches what is meant by "substantially reduced RNase H activity." *See, e.g.*, specification page 24, paragraph 0071. Therefore, the claim clearly comports with the requirements of 35 U.S.C. §112, second paragraph. Withdrawal of this portion of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 102

The Examiner has rejected claims 63, 21, 71, 82, 91, and 102 under 35 U.S.C. 102(a) as allegedly anticipated by Halvas *et al.*, (*J. Virology 74:*312-319 (January 2000), PTO-892, Document U). Applicants respectfully traverse this rejection.

The Examiner has taken the position that Halvas *et al.* teach M-MLV reverse transcriptase which has been mutated to increase fidelity. Applicants respectfully disagree. It appears that the Examiner has misinterpreted the disclosure of Halvas *et al.* Halvas *et al.* clearly show that mutations at valine 223 to methionine, serine or alanine *increased the mutation frequency*. This increase in mutation frequency actually indicates a decrease in fidelity of the mutants. See, page 316, Table 2. Applicants' position is supported by Kaushik *et al.* (*Biochemistry 39*:5155-5165 (published on the web April 7, 2000), IDS document AT36) who teach that valine 223 mutation to methionine results in a more error-prone phenotype. See, page 5164, column 1, lines 33-35, referring to Halvas *et al.* as reference number 69. Therefore, Halvas *et al.* teach mutations of M-MLV at valine 223 with decreased fidelity according to the present invention. *See, e.g.*, specification page 19, paragraph 0059, which discloses that an RT with increased fidelity

refers to an RT having an increase in accuracy of polymerization. Clearly, Halvas *et al.* do not anticipate the invention as claimed. Withdrawal of this rejection is respectfully requested.

Other Matters

Applicants gratefully acknowledge the Examiner's indication that no references were found teaching or suggesting claims 11-20, 22, 64-70, 72-81, 83-90, 92-101, and 103-120. Applicants respectfully submit that the presently pending claims 11-22 and 63-120 are now in condition for allowance. Thus, an expedited notice of allowance is respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Robert W. Esmond Reg. No. 47,473
Attorney for Applicants
Registration No. 32,893

Date: April 3, 2003

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600

Version with markings to show changes made

The following claims have been amended:

63. (Once amended) An M-MLV reverse transcriptase which has been mutated to increase fidelity compared to the corresponding unmodified reverse transcriptase, with the proviso that said mutation is not at amino acid position Tyr222.

111. (Once amended) The reverse transcriptase of any one of claims 63, 71, 91, and 107, wherein said reverse transcriptase has [reduced or] substantially reduced RNase H activity.